Functional characterization of mutational load in nuclear reprogramming and differentiation

Grant Award Details

Functional characterization of mutational load in nuclear reprogramming and differentiation

Grant Type: Basic Biology III

Grant Number: RB3-05083

Project Objective: The overall objective is to measure the mutational load introduced during reprogramming and differentiation, and to analyze the functional significance of such mutations.

Investigator:

Name:	Kun Zhang
Institution:	University of California, San Diego
Type:	PI

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,295,318

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title:	Functional characterization of mutational load in nuclear reprogramming and differentiation
Public Abstract:	One of the most potentially powerful aspects of regenerative medicine is stem cell therapy. In this therapy, healthy tissues derived from stem cells will be implanted into patients with damaged tissue in order to restore function. However, there is currently a risk of immune rejection. Human induced pluripotent stem (hiPS) cells have the potential to revolutionize regenerative medicine. By reprogramming a patient's own cells into pluripotent stem cells, stem cell therapies can be performed with little to no risk of rejection. However, this nuclear reprogramming process is not well understood at a mechanistic level. Also, all procedures developed to date use cancer-related genes. This has raised fears that current hiPS cells could potentially have a high cancer risk if used therapeutically. In this proposed research, we intend to study the mutation load associated with reprogramming and the functional consequences of the mutations. We will use the obtained knowledge about transformation to develop safer methods of generating hiPS cells. We will perform large-scale screening of somatic mutations that have potential deleterious effects during the reprogramming of human primary cells into hiPS cells, and the differentiation of hiPS cells into somatic cell types. We will also characterize whether mutations occurred have any function, including the increase of cancer risk. These information will help us to understand how do the mutations occur and propagate. This proposed project will not only help us to gain additional mechanistic insights on nuclear reprogramming, but also allow great progress towards functional stem cell therapy, as safe hiPS cells will be available for therapeutic use.
Statement of Benefit to California:	Over the past decade, California has made great progress in stem cell research thanks to Proposition 71. Research into stem cell properties and applications has made the promise of regenerative cell therapies almost a reality. Human induced pluripotent stem (hiPS) cells offer the promise of treatments or cures for diseases that affect millions of people without a risk of immune rejection, including Alzheimer's disease, heart disease, organ failure, and spinal cord injury. However, before these cells can be used therapeutically in the clinic, a better understanding of the mechanisms of generating hiPS and the safety of the resultant cells must be gained. Our work will greatly improve understanding of the reprogramming process with respect to genomic mutations and integrity by determining the relative safety of a variety of available hiPS reprogramming techniques. We will work towards creating hiPS reprogramming methods that have been proven to be non-tumorigenic. Through this research, we hope to clear one of the biggest hurdles stopping hiPS cells: the risk of cancer. Due to the huge potential of stem cell therapies in regenerative medicine, this work has applications to a large number of diseases and genetic disorders that affect Californians, from infants to senior citizens.